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Hormesis can enhance agricultural sustainability in a changing world

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ABSTRACT

Considerable evidence has emerged that low-dose challenges induce adaptive responses that protect organisms from preceding or succeeding toxic effects, endogenous aging activities or exogenous challenges/threats via conditioning processes. These principles indicate that pre-post conditioning processes can affect the theoretical foundations and practice of agricultural planning and programs, creating the potential to optimize outcomes/performance, leading to more favourable cost-benefit relationships. These developments can be applied to agricultural systems to reduce environmental change impacts, enhance resistance to microbes and pests, and increase productivity at far lower costs, helping to enhance agricultural sustainability in a "changing world". However, care should be exercised to account for risks that could be associated with the incorrect use of hormesis-based solutions and for regulatory issues that may arise. More caution should be taken regarding risks and regulatory as well as commercial difficulties that will likely hamper achieving greater agricultural sustainability.

1. Introduction

Reducing environmental impacts, securing food supplies, and improving agricultural sustainability is a core challenge in this world with changing environment and growing population (Ainsworth, 2016; Campbell et al., 2016; Jez et al., 2016; Sicard et al., 2017; Li et al., 2018). In the light of the increasing demands of food supplies under the pressure of changing environment, which limits plant yields and productivity (Oksanen et al., 2013; Bisbis et al., 2018; Feng et al., 2018; Mills et al., 2018) and threatens food quality (Loladze, 2002, 2014; Myers et al., 2014), Jez et al. (2016) enlightened an innovative path where technologies and approaches ranging from molecular to ecosystem levels are integrated into plant biology. While this and other ideas and paths enlightened by plant biologists over the decades offer an optimistic perspective, only some[1] of the several biotechnological "promises" made in the 1990s had the expected impact (Gressel and Dodds, 2013). This raises the issue of why so many seemingly good ideas were unable to have successful societal translations and what do scientists need to do differently to reach a better impact from such efforts.

To secure agricultural sustainability, it is a matter of utmost importance to understand how plant biology functions under stress. In this Perspective, we take a look at recent advancements in plant biology from the viewpoint of dose-response, and particularly that of hormesis, to provide a perspective for hormesis-based interventions in agriculture and food systems with the ultimate goal of enhancing agricultural sustainability in a changing world.

2. The dose-response and hormesis

Dose-response, i.e. how plants cope with stresses and their dose fluctuations, is a central evolutionary challenge and perhaps the most important one to understand how plant biology functions under stress, what its plastic limits are, and how the productivity and yields can be optimised (Calabrese and Mattson, 2017). The dynamic of such challenges becomes biologically described in the articulation of the dose-response. In fact, the dose-response is the "biological integrator" showing how organisms adapt to challenges. Thus, knowledge of the dose-response can provide valuable insights into often shrouded biological processes that lead to adaptation and enhanced survival prospects (Calabrese and Mattson, 2017; Agathokleous et al., 2018a). Not surprisingly, evolutionary processes have selected for traits that

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[1] e.g. the HarvestPlus program on the biofortification of staple foods (Bouis and Saltzman, 2017).

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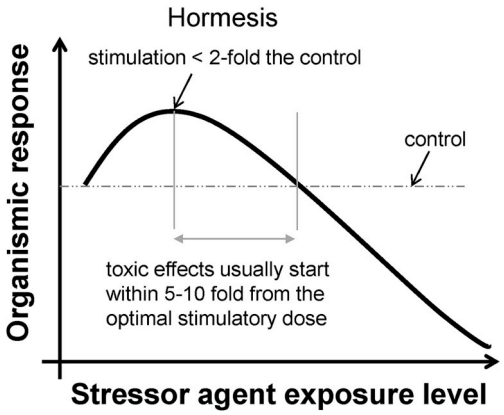

Fig. 1. Hypothetical hormetic dose-response model.

enhance coping with environmental stressors. These coping "skills" are reflected in the nature of the dose-response relationship. In addition to the coping "skills", dose-response relationship can be studied to identify and define risk zones of overdosing, via the estimation of certain *points of departure*, i.e. doses that correspond to some or no change in the biological response. Such risks may also be caused by biotic interactions as well (e.g. herbivores, diseases, microorganisms), which makes the risks even more difficult to predict in more or less uncontrolled systems, such as agricultural fields or animals that move across environments and are exposed to varying environmental conditions (Gressel and Dodds, 2013; Agathokleous, 2018; Agathokleous et al., 2019a).

The hormetic response with consistent quantitative features of amplitude and width (Fig. 1) is seen as a general evolutionary–biological strategy by which cells, organs and organisms optimally acclimate to low doses of stressor agents. The hormetic dose-response is also the central strategy by which preconditioning/priming occurs in plants and animals, showing the same quantitative features of hormetic dose-responses without preconditioning (Calabrese, 2016). The preconditioning concept was first shown in a series of some 48 experiments in the 1920s involving the effects of X-rays on lentil growth (Ancel and Lallemand, 1928). A later study provided a remarkable demonstration of the hormetic dose-response within the preconditioning framework for plant growth, exposing plants to seven conditioning doses of ionizing radiation prior to a challenging dose (Pape, 1950), with quantitative features similar to later studies (Cedergreen et al., 2007; Calabrese and Blain, 2011; Agathokleous, 2018; Agathokleous et al., 2018b). These early findings have been reaffirmed and extensively extended over the last two decades (Cedergreen et al., 2007; Calabrese, 2016; Agathokleous, 2018; Agathokleous et al., 2018a,b, 2019a).

The hormetic perspective provides the first quantitative description and underlying explanation for the magnitude of a type of biological plasticity at all levels of biological organization for plants and animals, showing the amount of "gain" there is in the system (Calabrese and Mattson, 2017). The implications of this hormesis-based dose-response revolution are considerable, with vast potential applications in medicine, public health, and agriculture, showing the degree and limits to which biological performance can be increased. The implications of the hormetic quantitative feature extend to all biological situations that involve low levels of chemical, radiological, mechanical or physical stressors.

3. Stress/adaptation biology and current regulatory hazard assessment

Stress or adaptation biology is often lost in animal and plant toxicology hazard assessment protocols where the emphasis is placed on exposure to high doses and often without a repeat measure or time component (Bogen, 2016; Agathokleous et al., 2018a). These general hazard assessment strategies are driven by governmental regulatory agency agendas, linked to low-dose modelling by extrapolating findings from high to low doses (Calabrese, 2011, 2017a, 2013; Bogen, 2016). In this process, much biological understanding is lost and low-dose predictions become at best uncertain and possibly incorrect especially when extrapolations extend over several orders of magnitude of dose.

The current regulatory framework denies not only the possibility of adaptive responses but also that low doses of toxic agents may induce overcompensation responses, in which the adaptive response repairs all the induced damage as well as spontaneously occurring background damage (Calabrese, 2001). In such cases, there is a net overall reduction in damage, i.e. a net benefit from the low-dose stress (Azzam et al., 1996). However, the past two decades have witnessed that adaptive responses are widespread, independent of biological model, endpoint and inducing agent (Calabrese, 2008, 2010; Calabrese and Blain, 2011; Calabrese and Mattson, 2017; Agathokleous et al., 2018a). Of practical significance is that such low-dose adaptive responses are often hormetic-biphasic dose-responses rather than the threshold or linear models that are used by guide regulatory agencies in their hazard assessment and policy-based activities (Calabrese, 2017b; Agathokleous et al., 2019b). This biologically untenable situation has created the need to better understand the nature of biological stress within the context of the dose-response, especially at low doses, and has led to a type of dose-response revolution.

Regulatory agency risk assessment actions have long institutionalized the use of the threshold and linear dose-response models for chemicals and radiation risk assessment, in many respects ignoring the possibility of adaptive responses and overcompensation responses and how they may be reflected in the dose-response (Calabrese, 2013, 2017a; Bogen, 2016; Agathokleous et al., 2019b). In fact, the U.S. Environmental Protection Agency (EPA) has even excluded the possibility of adaptation responses in their risk assessment process (Calabrese, 2006). However, for the first time, the U.S. EPA is now examining the possibility to consider non-linear dose-response relationships beyond threshold in its risk assessment procedures (Agathokleous et al., 2019c), a positive step that provides an important perspective for successful application of hormesis.

4. Hormesis and plant biology

Hormesis is a highly generalisable phenomenon occurring across biological organisms (Calabrese and Blain, 2011; Calabrese and Mattson, 2017). While the re-assessment of the literature for hormesis in plants delayed compared to that in animals and other organisms, efforts put mainly in the last ten years revealed accumulated empirical data (> 5000 records) to prove the hypothesis that toxic substances at low doses/concentrations can enhance growth and productivity. These include testing from many inducing agents, species, and endpoints, providing a multi-dimensional body of data as a basis for generating testable models that can predict optimal doses under a range of environmental conditions and for a range of endpoints (Calabrese and Blain, 2011; Garzon and Flores, 2013; Gressel and Dodds, 2013; Poschenrieder et al., 2013; Vargas-Hernandez et al., 2017; Agathokleous et al., 2019a,b,c,d; Brito et al., 2018; Morkunas et al., 2018). Numerous natural and synthetic chemical substances, physical stressors (e.g. irradiation and temperature) and anthropogenic environmental contaminants (soil and gaseous) in terrestrial and aquatic systems, such as metal ions, ground-level ozone, nitrogen deposition and human and veterinary pharmaceuticals, can induce hormesis in plants (Calabrese and Blain, 2011; Poschenrieder et al., 2013; Agathokleous, 2018, Agathokleous et al., 2018b, 2019b,c,d,e). This response is reflected to a number of core physiological processes, such as photosynthetic rate, Hill reaction activity, PSII efficiency and chlorophyll content, whose responses are eventually reflected to similar hormetic responses in yields and productivity; however, the exact molecular mechanisms at species or genotype levels remain poorly

understood and this gap should be filled before any application into the agricultural practice (Agathokleous et al., 2018b, 2019b,d). With the expansion of the body of evidence for hormetic dose-response relationships, and the thereby need for modelling, models have been also developed, and now exist, for predicting hormesis induced by single agents or mixtures of agents (Liu et al., 2011; Belz and Piepho, 2015, 2017; Zou et al., 2013).

So, what do these practically mean for the field of plant biology?

- Low doses of stress agents, including emerging contaminants at global scales, can be expected to increase the growth of most plant species. This is the case for crops, weeds and other plants (Cedergreen et al., 2007; Velini et al., 2010; Agathokleous et al., 2018b, 2019b; Brito et al., 2018). This should not be necessarily considered as a "beneficial" effect in uncontrolled environments because such a growth could occur at the expense of plant defence capacity, e.g. against pathogens and herbivores, which could finally lead to negative effects.
- Each species will display a unique optimal stimulatory zone, shifting either to the left or right on the dose-response spectrum (Agathokleous et al., 2019e), suggesting also unpredictable risks in uncontrolled environments where groups of plants co-exist. For instance, weeds may outperform the cultivated plants. For these reasons, target-specific applications should be considered in uncontrolled environments, after species-specific dose-response screenings of the vegetation co-existing in given field conditions.
- The quantitative features of these biphasic dose-responses will be such that the stimulation will be less than 2-fold and that toxic effects will start to occur in most cases within 5–10 fold from the optimal stimulatory dose (Calabrese and Blain, 2011; Agathokleous et al., 2018b, 2019d). The small distance from the optimal stimulation point to the toxicity point suggests risks from the application of the concept when applied in uncontrolled environments where plants are exposed to cocktails of environmental contaminants or under harsh environmental conditions. For safe application of the concept under this scenario, assessment of the local environmental conditions should be conducted, and preliminary targeted dose-response screening should simulate similar environmental conditions.
- Low doses of complex mixtures can also affect hormetic responses but they too are constrained by the limits of biological plasticity to have a stimulatory response commonly less than twice the control group response (Belz et al., 2008; Ge et al., 2011; Belz and Piepho, 2017). This suggests that the concept of hormesis has a potential for successful application in environments with cocktails of stressors. Preliminary targeted dose-response assessments should account for effectiveness in inducing desired effects, and avoiding undesired ones, when the stimulation-inducing agent acts as a component of a mixture of agents.
- The maximum response to the optimal dose describes and defines the amount of "gain" there is in the biological system, providing a quantitative estimate of biological plasticity (Calabrese and Mattson, 2017). Assessment of the maximum response of key endpoints (e.g. photosynthesis and chlorophyll *a* fluorescence) at regular intervals, most likely weekly, would aid in effectively inducing desired effects and in combating risks for negative effects that may associate with accumulated stress. For example, an unusual drop in the maximum response could indicate accumulated stress due to incorrect application of the concept and/or local environmental events, and, thus, the application of the concept should be suspended for as long as needed or the applied dose of stress be reduced to help alleviate the damage in the framework of conditioning according to prior knowledge based on relevant assessments.
- Low doses of stress-inducing agents can upregulate adaptive mechanisms that mediate protection against subsequent threats within a defined time window, which typically is ≈ 7–10 days (Cedergreen, 2008; Calabrese and Mattson, 2017; Leak et al., 2018; Agathokleous et al., 2019b,d). The quantitative features of the preconditioning mediated protection follow the quantitative features of the hormetic dose-response (Calabrese, 2016; Calabrese and Mattson, 2017). These suggest that the application of hormesis may also protect plants against local environmental events that may occur unexpectedly, such as under unexpectedly high peaks in insect herbivore populations and ozone episodes.

5. Perspectives for enhancing agricultural sustainability in a changing world

The global food system faces a crisis with energy production, amino acids, micronutrients and specific macronutrients, especially amid the Sustainable Development Goals of the United Nations (UN) for ending all the forms of malnutrition (SDG2) by 2030 (Ritchie et al., 2018). Securing and increasing food supplies and overall improving agricultural sustainability are tasks of high priority so as to achieve the agricultural production targets of 2050 estimated by the Food and Agriculture Organization of the United Nations (FAO) due to increasing population (Jez et al., 2016). However, it is extremely challenging to achieve the 70% increase in agricultural production in the light of changing environments, such as drought and air pollution, that lead to significant suppression of agricultural productivity (Oksanen et al., 2013; Bisbis et al., 2018; Feng et al., 2018; Mills et al., 2018; Springmann et al., 2018) and threaten millions of peoples with malnutrition due to the potential depletion of minerals (Loladze, 2002, 2014; Myers et al., 2014). This situation may see no improvement if no significant technological changes and mitigation measures take place at planetary scale (Springmann et al., 2018). To this end, novel approaches are needed which will fully utilise the most up-to-date scientific knowledge of plant biology. The most up-to-date knowledge about dose-response plant biology provides a promising solution for increasing food supplies and enhancing agricultural sustainability.

The hormesis concept sees all living material as dynamic and adaptable, with the potential to use low-dose stress to their survival advantage. This concept can enlighten the study, evaluation, and assessment of environmental practices and risk assessment locally, regionally and globally. The characteristics of the hormetic dose-responses can have a central role in the process of hazard assessment, that is, the biological models selected, key features of the study design, such as the number and spacing of doses, the need for repeat measures, sample sizes, and other features. The hormetic model can also be used in the risk assessment process, having the capacity to properly assess harmful, neutral and potentially beneficial outcomes [for a relevant review and references with differing opinions the reader may refer to Agathokleous et al. (2019c)]. These will lead to maximisation of plant productivity and food supplies under environmental change.

The hormesis concept can also be applied to the agricultural practice by different means. First, the concept of conditioning, a manifestation of hormesis, offers a perspective for enhancing the resistance to microbes and pests and increasing productivity at far lower costs (Morkunas et al., 2018). Plants can become beneficial of low-dose stress experienced prior to or after exposure to a threatening environmental condition, hence, reducing the impacts. The pre-conditioning promotes a stress defense machinery, whereas the post-conditioning creates a subtraction from background/spontaneous damage. Preconditioning (also called priming in plant science) was applied to seeds or plants and successfully enhanced tolerance to stress (Savvides et al., 2016; Agathokleous et al., 2019a). Second, hormesis offers a perspective for selective application as to the desired outcome/characteristics. For example, it can be utilised for enhancing the quality of food, increasing the production of particular phytochemicals either consumed directly or used for medical purposes, or increasing productivity/biomass and/or yields by exposing plants to selective doses of stress over defined time windows (Howitz and Sinclair, 2008; Son et al., 2008; Hadacek et al., 2011; Gressel and Dodds, 2013; Agathokleous, 2018;

Agathokleous et al., 2019b,d). Third, hormesis offers an important perspective to enhance yields via its implementation in bioengineering (Agathokleous et al., 2018c). Fourth, conditioning can be utilised in post-harvest engineering for enhancing the quality and longevity of agricultural products after harvest via enhancement of the defense machinery by low doses of stress such as ozone and heat (Agathokleous, 2018; Agathokleous et al., 2019b). These can increase food supplies, with a potentially higher nutritional value/quality.

Although hormesis offers an important perspective to enhance yields via its implementation in bioengineering (Agathokleous et al., 2018), as explained in section 4, there are known unknowns and possible risks with the wider application of hormesis-based interventions (or technologies) in agriculture and the food systems. Two concerns are:

- First, there may be risks when hormesis-based interventions are applied into uncontrolled environments as it happens with open fields (Pagano et al., 2015; Agathokleous et al., 2019d). Incorrect application of such interventions may lead to effects opposite than the desired ones, e.g. the plants may become more sensitive to pests and pathogens or even experience negative effects due to overdosing related to accumulated environmental stress that cannot be controlled (Gressel and Dodds, 2013; Agathokleous et al., 2019a). These suggest that preliminary toxicological dose-response assays simulating conditions similar to the local ones ideally would precede application to uncontrolled environments. In these assays, overdosing, sub-dosing [as there may be negative effects at yet sub-hormetic doses (Kim et al., 2018)], and stimulation of the virulence of local strains of pathogens (Lu et al., 2018) should be considered. Without this prior knowledge, the application of hormesis-based interventions and technologies would be less appropriate for uncontrolled systems but still potentially suitable for controlled systems (e.g. greenhouse).
- Second, it is unknown if the quality and nutritional value of agricultural products harvested from plants cultivated in field conditions with hormesis-based interventions would be equal or higher. More research should be directed towards this question. However, a remarkable base of postharvest biology and technology research shows that the quality and nutritional value of fruits and vegetables exposed to hormesis-based interventions and technologies, before or after harvest, can be increased (Minas et al., 2010; Cantin et al., 2012; Agathokleous, 2018). The post-harvest base commonly involves physical and gaseous agents, which cannot find easy application into the field. Therefore, hormesis-based interventions and technologies which make use of physical and gaseous agents can find successful application to controlled environments such as greenhouses (Cantin et al., 2012) but would be less efficient or inefficient in the field. For this reason, only chemical compounds would be applicable to field conditions. However, there is a need for pre-screenings of residues in the agricultural products.

The translation of basic research into real-world commercial products is not an easy task and hormesis-based interventions and technologies are not an exception (Gressel and Dodds, 2013). As hormesis-based solutions may require treatments every ≈7–10 days (Cedergreen, 2008; Calabrese and Mattson, 2017; Leak et al., 2018; Agathokleous et al., 2019b,d), the application into the practice could be difficult, but slow-release formulation of hormetic effectors might help to solve this issue (Gressel and Dodds, 2013). However, it is questionable whether industries will commercialise hormesis-based agrochemicals since there may not be the desired economic profits because of the lower amounts of agrochemicals needed and the potential dilution of high-concentrated agrochemicals by farmers themselves (Gressel and Dodds, 2013). RNA interference (RNAi) has emerged as a promising technology in functional genomics with a significant potential for environment-friendly crop improvement in the light of biotic and abiotic stress (Baum et al., 2007; Mao et al., 2011; Saurabh et al., 2014; Younis et al., 2014). RNAi technology relies on small interfering RNA molecules and micro RNAs for inducing genetic expressions in plants during their growth. Hence, RNAi may be viewed as an example for hormesis-based intervention with a high potential for commercial application.

Hormesis-based interventions and technologies may not enter the market in less than a decade because of the time needed to meet the requirements of the risk assessments and regulatory approval. The question is how this could be accelerated. Several “biostimulants” widely applied within the hormesis framework successfully enhanced plant yield and productivity and tolerance against stress (Savvides et al., 2016; Agathokleous et al., 2019a). This suggests that natural compounds may aid in accelerating the adoption of hormesis-based solutions and technologies in the agricultural practice, compared to synthetic chemicals. When seeking to have successful societal translations, scientists should attempt to find solutions that would be more society-friendly. It is our own view that society would be more open to the application of biologically derived hormetic additives (we do not think that there is someone who would like the idea of eating tomatoes from plants cultivated with “toxic heavy metals”). Furthermore, an excellent example that can serve as a basis for applying hormesis-based interventions and technologies into the agricultural practice is the agricultural application of rare earth elements, in the framework of hormesis, for improving yield and quality of cultivated crop plants in China over decades (Pang et al., 2001; Pagano et al., 2015; Agathokleous et al., 2019d). This proves that hormesis-based solutions can be something beyond a laboratory curiosity. Moreover, the rare earths research on “fertilization” effects and risks provides a fundamental base that can be utilised to accelerate the processes of risk assessments and regulatory approval (Pagano et al., 2015; Agathokleous et al., 2019d).

Based on the current dose-response knowledge, we here provide a candidate solution to the issue of food supplies that pertains to the environmental, social, engineering, and policy dimensions of agricultural sustainability. The hormesis concept permits fully integrative evaluations across the entire dose-response spectrum, providing the best opportunity for scientists and regulators to evaluate environmental factors. It also provides an opportunity for increasing the global food supplies and enhancing the socioeconomic development in Least Developed Countries. This concept offers a unique opportunity to combat developing food crises (Puma et al., 2018), particularly when applied in integration with other interventions (e.g. breeding for tolerance and enhanced yields, biotechnology and control of pests and diseases), following a systems approach.

Author contributions

Each author was fully involved in all aspects of the study and takes responsibility for the integrity and the accuracy of the study concept and work product. Initial drafting of the manuscript was done by EJC. Critical revision of the manuscript for important intellectual content was performed by EA. Each author has read and approved the manuscript for submission. EA revised the reviewed manuscript. EJC and EA reviewed the revised manuscript. Each author has read and approved the final manuscript.

Declarations of interest

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